

HUMAN CARDIAC
TRANSPLANTATION

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Reprinted from
THE JOURNAL OF THORACIC AND
CARDIOVASCULAR SURGERY
St. Louis

Vol. 55, No. 3, Pages 447-451, March, 1968

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(Printed in the U. S. A.)

Editorial

Human cardiac transplantation

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Editor's note: The electrifying news of Dr. Christiaan Barnard's technically successful heart transplant has aroused various reactions in the minds of both the medical profession and the lay public.

This brilliant achievement has many ramifications which should be placed in proper perspective. It is for this reason I invited Dr. Michael E. De Bakey to prepare an editorial for THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY.

Brian Blades, M.D.

On Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa, a human heart was transplanted for the first time. Using transplantation techniques that had previously been developed by scientists in experimental laboratories around the world, the surgical team, headed by Dr. Christiaan Barnard, removed a heart that was failing because of coronary occlusive disease from a 55-year-old man and replaced it with the heart of a 25-year-old woman shortly after her fatal injury in an automobile accident. Within minutes after completion of the procedure and cardioversion of the fibrillating transplanted heart, an effective heartbeat was restored. After a few brief periods of partial circulatory assistance with the heart-lung machine, the transplanted heart assumed its circulatory function and maintained adequate blood pressure to permit discontinuance of cardiopulmonary bypass. Disappearance of previous clinical signs of heart failure within 3 days after operation indicated that the transplanted heart was providing satisfactory cardiac output. The

patient reportedly made good clinical progress until the twelfth postoperative day, when some evidence of pneumonitis became apparent. Despite intensive treatment, the patient's condition rapidly worsened, and he died on the seventeenth postoperative day of extensive bilateral pneumonia.

Three days after the Cape Town operation, a surgical team in Brooklyn, New York, headed by Dr. Adrian Kantrowitz, transplanted the heart from an anencephalic infant to a 2½-week-old infant with tricuspid atresia, but the patient died 6 hours after the operation. On Jan. 2, 1968, Dr. Barnard performed his second cardiac transplantation in a 58-year-old man with congestive heart failure produced by coronary arterial disease; the donor was a 24-year-old man who had had a cerebral hemorrhage. At the time of this writing (Jan. 27, 1968), this patient is reportedly progressing satisfactorily. On Jan. 6, 1968, Dr. Norman Shumway did a similar procedure at Stanford University Medical Center on a 54-year-old man with similar heart disease and severe hepatic congestion. A series of complications necessitated three subsequent operations on this patient: one to control gastrointestinal bleeding, a cholecystectomy, and a vagotomy and splenectomy. The pa-

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tient died 2 weeks after transplantation. The fifth human cardiac transplantation was done on Jan. 9, 1968, by Dr. Adrian Kantrowitz on a 57-year-old man with coronary artery disease who received the heart of a 29-year-old woman who died of a brain tumor. This patient died 10 hours after transplantation. At this writing, therefore, only 1 of 5 patients who had cardiac transplantation is still living.

The immediate technical success of the first Cape Town procedure electrified the world and seemed to bring to reality the long-cherished hope that an incurably diseased and failing heart could be replaced. But the early death of this first patient and the failure of three of the four subsequent attempts brought a resurgence of questions previously posed about homotransplantation of vital organs, particularly of the heart. These questions have clinical, moral, ethical, legal, theologic, and psychologic implications, but they derive primarily from the limited available scientific evidence underlying recommendation of the procedure as *treatment* for certain forms of human cardiac disease. Assessment of the current state of human cardiac transplantation, based on laboratory experience, permits considerable divergence of opinion about its current clinical applicability.

Experimental studies in cardiac transplantation have been intensively pursued for some years in a number of laboratories throughout the world. Although the technical aspects of the procedure have been well developed for some time and fully described in scientific publications, long-term survival in animals has not been impressive. The first clinical application of the procedure took place in 1964 when Dr. James Hardy and his associates transplanted the heart of a chimpanzee into a 68-year-old white man who was in terminal heart failure caused by severe coronary atherosclerosis, but the patient survived only a few hours. In none of the clinical cases to date has the patient survived long enough to permit adequate observation or definitive conclusions. The only data on which future clinical trials

can be based are therefore experimental evidence in animal transplantation of the heart and clinical evidence in transplantation of the kidney and liver. Only about 20 per cent of the animals with transplanted hearts have survived 3 months, although a few have lived 6 months to a year. Clinical evidence in transplantation of the liver is limited to 5 patients, 2 of whom died within a few months and the other 3 of whom have been living only a short time since operation, the longest survival being 5 months. In the case of the kidney, in which experience has been the greatest, homotransplantation between unrelated donors, until recently, has yielded an over-all survival rate of only 21 per cent at the end of the first year after operation. Within the past year, improved histocompatibility testing, use of antilymphocytic serum or antilymphocyte globulin, corticoids, and Azathioprine have reportedly increased survival rates to as high as 95 per cent at the end of a year in a few medical centers. Although some workers believe that rejection of the heart is easier to suppress than that of other organs, no clear-cut scientific evidence has yet been advanced to support this impression. In the light of current scientific knowledge, therefore, indications for transplantation of the heart in human beings are restricted.

The major critical problems that require solution to make the procedure generally applicable and practical as a method of treatment are concerned with the rejection phenomenon and the availability of donor hearts. Current knowledge of methods of suppressing the rejection phenomenon in human organ transplantation is derived largely from experience with the kidney and the rather meager experience with the liver. To what extent these methods will serve a similar purpose and will be effective in human cardiac transplantation is not known. Methods of suppression in animal renal transplantation have yielded much less effective results than in human renal transplantation. Similar differences may exist in the case of the heart, and the relatively low

survival rates in animal cardiac transplantation may therefore not be applicable to human beings.

Two other aspects of this problem have significant bearing on cardiac transplantation as it differs from renal transplantation. First, whereas the patient with a renal transplant may survive several episodes of rejection, even when a considerable part of the functioning renal tissue has been destroyed by this process, partial destruction of the heart may not permit sufficient cardiac function to keep the patient alive. Second, even with complete destruction of a transplanted kidney, the patient can be kept alive temporarily by means of the artificial kidney until another kidney can be transplanted. Thus, whereas the life of the patient is not necessarily threatened by failure of a transplanted kidney, it is obviously imperiled by failure of a transplanted heart. This threat emphasizes the urgent need to develop an artificial heart, even if only for temporary maintenance of life.

As in all organ homotransplantation, the complexity of the surgical procedure is magnified by the necessity of a suitable donor. Since the most practical donors at this time are considered to be young, healthy victims of fatal injuries or diseases that do not affect the heart, awaiting a satisfactory donor may delay transplantation for months, and the critically ill cardiac patient may die in the interim. When a potential donor is found, consent must be obtained, extensive histocompatibility and other studies must be done, and the donor heart must be removed, all within the brief period required to permit restoration of cardiac viability after the donor's death.

The moral, ethical, legal, and psychologic implications of human cardiac transplantation will undoubtedly be much more far-reaching than anticipated from present brief experience. The issues must be thoroughly analyzed, human values reconsidered, and satisfactory answers sought in the light of reason rather than in the heat of emotions. Clichés, irrelevancies, and capricious injunctions must not be allowed to thwart sane

judgment. Should medical scientists abrogate their responsibility to their patients and to society to resolve such issues when they arise, they can expect restrictions to be prescribed from without.

The clinical and legal definitions of death impose grave responsibilities on the surgeon in removal of the donor's heart. Fully informed consent of both recipient and donor, or of next-of-kin, must, of course, be obtained. The surgeon must scrupulously guard against taking inadvertent advantage, for purely experimental purposes, of the eagerness of a desperately ill patient or his family to consent to almost any procedure suggested by the physician. He must be certain that the proposed heart transplantation is clinically and therapeutically indicated. He must also be certain, beyond any conceivable doubt, that nothing further can be done to save the donor's life. This judgment should be made independently by physicians who are not members of the transplantation team. Because of the brief interval permissible between death of the donor and transplantation of his heart to the recipient, the definition of death becomes crucial. The controversy has resumed on this point, with proposals for a new criterion of death based, for example, on electroencephalographic findings and other demonstrable evidence of cessation of vital cellular function. The legal, moral, and theologic aspects of this problem are intricate and formidable, but not impenetrable.

In certain clinical circumstances, an extravagant operative risk may, of course, be justified. Clinical trial of cardiac transplantation may therefore be warranted when it offers the only possible chance for survival of the patient. The patient with such severe cardiac failure that no curative or palliative treatment is known and in whom death seems imminent by all current medical evidence, but who might survive if cardiac function could be restored, would therefore seem to be a suitable candidate for such a clinical trial. The possibility of minimizing the rejection phenomenon by currently available methods of tissue typing and

the recent improvement in survival rates in renal transplantation are plausible arguments in support of further clinical trials. With existing data and knowledge, however, the clinical indications for this procedure must be carefully circumscribed and the patients painstakingly screened. Only highly skilled cardiovascular investigative teams with extensive experience in animal cardiac transplantation, as well as in human renal transplantation, should embark on clinical cardiac transplantation at this time. Obviously, this limits the procedure to specialized clinical research centers in which these activities are being intensively conducted.

All medical and surgical procedures performed for the first time on human beings are, of necessity, based on experimental evidence from the laboratory. Even when the merit of a therapeutic procedure has been unequivocally established in animals, its clinical value remains unknown until it is applied in a human being. As every medical scientist knows, extrapolation of animal data to human subjects can be extremely hazardous, and clinical merit must await clinical trial. Such was the case in the first human renal transplantation and, for that matter, in the first successful pneumonectomy, the first successful resection of coarctation, the first successful aorto-pulmonary shunt, the first successful open-heart operation with use of cross-circulation, the first successful open-heart operation with use of the heart-lung machine, and the first successful resection and graft replacement of an aneurysm of the aortic arch. In the light of medical history, laboratory evidence for the application of new procedures to human beings does not have to provide *final* answers, but in the past has been based on sound scientific, clinical, and surgical judgment. These abstract criteria hold today.

The South African experiment is a significant phase in human cardiac transplantation primarily because of its unequivocal confirmation that the pumping function of the human heart can be successfully replaced. Whether satisfactory function of the sub-

stitute can be maintained for prolonged periods remains to be determined. In supporting the conviction of many workers that total replacement of the heart is feasible, the South African experiment points up the need and, indeed, urgency for more energetic research to achieve this ultimate objective. Toward this end, investigation must be intensified to find better methods of controlling the rejection phenomenon and of suppressing the antigenicity of donor tissue. Satisfactory methods of preserving potential donor organs must be vigorously sought. The problems of demand exceeding supply must be confronted even if all current technical and clinical obstacles are overcome and human cardiac transplantation becomes an established therapeutic procedure. In this country alone, several hundred thousand patients need partial, temporary, or total permanent replacement of their failing hearts. Since only several thousand acceptable donors can be anticipated under present circumstances, some other means of helping these patients must be sought.

Experience with various artificial prostheses, including heart valves, aortic and other vascular grafts, as well as the left ventricular bypass pump and other heart assistors, suggests that mechanical replacement of the heart is both feasible and practical; this approach eliminates any delay in replacement and circumvents many of the moral, ethical, legal, psychologic, and other troublesome complexities of transplantation. As indicated previously, moreover, an artificial heart, comparable to the artificial kidney is urgently needed to sustain life when a human cardiac transplant fails. Such a safeguard would enhance the acceptability of the procedure clinically as well as ethically. Research directed toward refinement and improvement of cardiac assistors and development of mechanical pumps for total replacement of the heart must therefore be energetically pursued.

Since the physician can never afford to delay medical treatment until knowledge is complete and risk is entirely removed, he

must apply current knowledge cautiously and judiciously, weighing the benefits against the hazards, in his efforts to relieve suffering and cure disease. Continued clinical trials are therefore necessary, but only after the most sober deliberation and the most prudent consideration of all present evidence of their potential usefulness and limited scope. The indications for transplantation of the human heart at present must therefore be carefully delineated. The

competing risks must be thoroughly assessed: application of a procedure, results of which are not completely known, against withholding of a clinical trial that may save the patient's life. Such assessment requires the sagest, most deliberate judgment, based on extensive clinical experience in the cardiovascular field and on the knowledge and skills acquired in the specialized cardiovascular research and transplantation centers of the world.